

# Premalignant gastric lesions, Immunotherapy and Chinese medicine

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## Abstract

Gastric cancer is a common gastrointestinal malignancy, and reducing the incidence and mortality of gastric cancer is a major public health problem that needs to be addressed urgently. The application of pharmacological interventions for precancerous states and lesions of the stomach is one of the important aspects of gastric cancer prevention, and recent studies have shown that Chinese medicine has unique advantages in this regard. In this review, we list the possible targets and mechanisms of action of TCM acupuncture or herbal formulations by compiling the understanding and therapeutic tools related to the treatment of gastric precancerous lesions, with a focus on their immunotherapeutic mechanisms. This study contributes to the understanding of the potential role of TCM multi-target and multi-pathway interventions of the immune system in gastric precancerous lesions, and also provides an outlook on the possible new targets and pathways.

## Keywords

gastric precancer, signaling pathway, immune mechanism, Chinese medicine, target, network pharmacology

According to the Global Cancer 2020 statistics released by the International Agency for Research on Cancer (IARC), it is known that gastric cancer ranks 5th in incidence and 4th in mortality of malignant tumors [1]. According to China Cancer 2020 statistics, gastric cancer ranks as the 3rd newest case in China, and 43.9% of new gastric cancer cases and 48.6% of deaths from gastric cancer worldwide occur in China [2]. With the acceleration of aging and urbanization, unhealthy life patterns and high-pressure work environment, the risk factors of gastric cancer are gradually increasing and the burden of gastric cancer will intensify. Therefore, the prevention, control and treatment of gastric cancer are more important.

Gastric precancerous lesions (GPLs) are a pathological state in which the gastric mucosa transforms from normal to gastric cancer, mainly referring to moderate to severe heterogeneous hyperplasia and incomplete colonic-type intestinal hyperplasia, which is an important stage of pre-cancerous gastric lesions. Capturing the signals of pre-cancerous gastric lesions, timely and effective symptomatic treatment and interrupting the development of the disease can efficiently reduce the incidence of gastric cancer. Modern medicine mostly believes that the occurrence and transformation of gastric cancer is related to *H. pylori* and autoimmune mechanism, and the

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treatment is mostly based on eradication of HP, acid suppression and antioxidant, which have limited effect on stopping the transformation of gastric mucosa [3]. Since ancient times, Chinese medicine has the idea of prevention before disease and prevention after disease, which can take advantage of its own advantages to control and even reverse the disease development process in a timely and effective manner. In this paper, we will take the clinical trials and experiences of Chinese medicine and acupuncture against GPLs as observation points, explore the ways of TCM to regulate gastric precancerous lesions, and summarize the immune mechanism of TCM against GPLs. It will provide a clear etiological mechanism for TCM to seek precancerous lesions, with the aim of precise and symptomatic treatment, improving clinical efficacy and reducing patients' pain.

## **1. Modern medical research on the mechanism of GPLs**

GPLs is a disease development process, the complete pathogenesis study is not clear, this paper will discuss from inflammatory factors, signaling pathways, oncogenes and tumor microenvironment (Figure 1).

### **1.1 Inflammatory factors are altered to stimulate the inflammatory microenvironment and promote inflammatory cancer transformation**

Inflammatory cells and epithelial cells produce reactive oxygen/nitrogen species (ROS/RNS), and chronic inflammation causes various damages to nucleic acids, proteins and lipids through ROS/RNS production. The persistence of chronic inflammation promotes the growth of gastric cancer cells and increases the chances of gene mutation, which eventually leads to the transformation of benign tumors to malignant ones [4].

Interleukins (IL) are involved in the expression and regulation of immune responses and are currently well studied as IL-1, IL-4, IL-6, IL-8 and IL-10. IL-1 is a multifunctional cytokine that controls inflammatory, immune and hematopoietic functions. In the tumor microenvironment, IL-1 promotes cell expression and advances tumor invasion and progression [5]. IL-4, like most cytokines, affects multiple target cells in multiple ways. IL-6 promotes host defense after infection and tissue injury. IL-8 and related cytokines are produced after infection, inflammation, ischemia, and trauma [6]. IL-10 regulates the immune response during organismal defense and plays an important role in autoimmune diseases, inflammatory diseases and cancer [7].

Tumor necrosis factor alpha (TNF- $\alpha$ ) is involved in immune system maintenance and homeostasis, inflammation and host defense [8]. Numerous studies have confirmed the involvement of TNF- $\alpha$  in several pathological processes such as gastric carcinogenesis, cell proliferation, gastric cancer invasion and metastasis, epithelial mesenchymal transformation, and neovascularization [9].

COX-2 plays an important role in protecting gastric mucosa and promoting sore healing. COX-2 expression is low in normal physiological state, but it is highly expressed in inflammatory environment and stimulated by tumor cells [10]. It was found that reducing COX-2 protein expression in gastric mucosa helps to improve gastric mucosal inflammation, not only relieving patients' clinical symptoms but even reversing the pathological process of mucosal atrophy and intestinal epithelial metaplasia [11].

The persistence and further development of inflammatory factors lead to the formation of an

inflammatory microenvironment in vivo, and inflammatory factors link inflammation to tumor with the help of activation and initiation of signaling pathways such as Rho/ROCK and NF- $\kappa$ B, creating an inflammatory-cancerous transformation mechanism that drives tumorigenesis and development.

## **1.2 Abnormal expression of pathways, altered signaling, and multiple pathways assist the process**

In recent years, molecular signaling pathways have been increasingly studied, providing new directions for the pathogenesis of gastric precancerous lesions. the NF- $\kappa$ B pathway regulates the inflammatory response, regulates proliferation, anti-apoptosis and angiogenesis, and it plays different regulatory mechanisms in different cellular environments. in the complex tumor microenvironment, NF- $\kappa$ B or with other molecular pathways promote each other and jointly participate in the occurrence and development of PLGC [12]. MAPK is mainly present in the cytoplasm and mediates a variety of cellular responses and intervenes in cell growth and apoptosis [13]. p38, as a class of proteins in the MAPK pathway, is involved in regulating the signaling of inflammatory, tumor and various stress pathways in the body. EGFR regulates mucosal cell growth and development, repairs damaged mucosa, and participates in the differentiation, proliferation and maturation of gastrointestinal epithelial cells, while EGFR overexpression accelerates the heterogeneous proliferation of epithelial cells [14].

The Wnt signaling pathway, JAK/STAT signaling pathway, and TGF- $\beta$ /Smad signaling pathway [15-17] are involved in cell growth, proliferative transformation, and other physiological activities, and are among the most common interfering signaling pathways during tumor formation and progression. Signaling pathways affect each other and interact with each other, so prevention and treatment of PLGC should intervene and regulate multiple signaling pathways at the same time [18].

## **1.3 Activation of proto-oncogenes and inactivation of oncogenes, disrupting the cell proliferation-apoptosis balance**

Genes regulate tumor generation, reproduction and apoptosis. The activation of proto-oncogenes and inactivation of oncogenes lead to abnormal signaling pathways, which are important causes of carcinogenesis [19]. abnormal proto-oncogenes such as  $\beta$ -catenin, cyclinD1, C-myc, ras gene family, tyrosine kinase transmembrane receptor (C-met), tyrosine kinase cell surface receptor (C-erbB2) activation, stimulating cell proliferation and promoting tumorigenesis. Down-regulation and inactivation of oncogenes levels such as phosphatase gene (PTEN), Runt-related transforming growth factor 3 (Runx3), Bcl-2, P16, P53, P21, etc., induce proliferation and migration of cancer cells. Mutations or malfunctioning expression of tumor-associated genes promote tumor cell proliferation, disrupt the proliferative and apoptotic homeostasis of the cell cycle, and drive tumor development [20].

Free  $\beta$ -linked protein enters the nucleus and binds to T-cell factors, initiating downstream target gene transcription and activating the Wnt/ $\beta$ -linked protein signaling pathway, leading to tumorigenesis [21]. cyclinD1 plays a key role in cell proliferation and is a key protein regulating the G1 to S phase transition [22]. As a DNA-binding protein, the oncogene c-Myc plays an

important role in regulating cell growth and metabolic cycles, stimulating angiogenesis, and promoting malignant transformation, proliferation, and differentiation of recombinant cells [23]. As the only tumor suppressor gene that dephosphorylates lipids, PTEN plays a key role in cell cycle arrest, cell invasion, migration and apoptosis [24]. Methylation of the tumor suppressor gene RUNX3 is considered to be a hot topic of current research. Once methylation occurs, RUNX3 expression is suppressed, which affects apoptosis and promotes tumor development [25]. The bcl-2, a suppressor gene, prolongs cell life and increases cell numbers by resisting cell death [26]. mutation or inactivation of P16 will shorten the G1 phase of the cell cycle and cells will enter the S phase prematurely, thus promoting uncontrolled cell proliferation [27].

#### **1.4 Tumor angiogenesis, tumor environment formation**

Sustained angiogenesis is one of the essential features of tumors, and factors associated with PLGC angiogenesis include vascular endothelial growth factor (VEGF), angiopoietin (Ang), and epidermal growth factor (EGF) [28]. Inhibition of VEGF overexpression improves the hypoxic state of gastric mucosa, inhibits microangiogenesis, and alleviates or even partially reverses gastric mucosal enteric and heterogeneous proliferative lesions [29].

The acidic tumor microenvironment provides favorable conditions for malignant tumor growth and local invasion. Aerobic glycolysis is one of the important energy metabolic features of cancer cells [30]. Excess H<sup>+</sup> is produced during glycolysis, which contributes to the acidification of the microenvironment, and the low pH extracellular microenvironment promotes cell invasion, metastasis, and proliferation [31].

## **2. Recognition of GPLs in Chinese medicine**

Gastric precancerous lesions are a kind of modern medical understanding of the progression of gastric cancer. In Chinese medicine, according to the symptoms of disease development, they are summarized as "stomach pain", "gastric regurgitation", "vomiting" and so on. In order to better analyze the evidence, various medical doctors have analyzed its etiology and pathogenesis. The development of gastric cancer is a comprehensive result of multiple factors and stages. The development of gastric cancer is closely related to the deficiency of positive energy of the body and the invasion of external evil. The deficiency of positive energy of the body refers to the weakness of spleen and stomach and the dysregulation of internal organs. External evil refers to qi stagnation, blood stasis, phlegm coagulation, stasis poison, damp heat and so on.

Zhang Jinyue has pointed out that "regurgitation, food can still enter, to Yang deficiency can not be transformed, can be warm can be tonic", so it can be seen that ancient doctors have long recognized the weakness of the spleen and stomach as the root of gastric diseases. Lu Zhi-Zheng believes that deficiency of the spleen and stomach and dysregulation of transportation and transformation are the basis for the development of stomach cancer, pointing out that the spleen and stomach are the source of qi and blood production and do not operate smoothly, which can easily lead to deficiency of positive qi, and then produce pathological symptoms such as stagnation and phlegm obstruction. Ye Tianshi said, "At the beginning of the disease, qi is knotted in the meridians, but after a long period of illness, blood is injured into the ligaments." Xu Jingfan also suggested that the evolution of pathological evidence from gastritis to gastric cancer is based on "blood stasis". "Evil is distant from the stomach and the stomach, which becomes poisonous

after a long period of time", and heat and poison stasis are also key factors in its development. In conclusion, stomach cancer is the result of internal weakness of spleen and stomach, dysfunction of internal organs, plus the joint action of phlegm, stasis, heat and toxin, etc. Therefore, its pathological mechanism is a comprehensive response of multiple pathological processes intertwined.

### 3. Chinese medicine treatment

Under the influence of holistic concept, Chinese medicine is characterized by evidence-based treatment. In the treatment of gastric precancerous lesions, it has always focused on the combination of supporting the righteousness and eliminating the evil, and the focus of each school of treatment differs, but the overall treatment method is mostly to cultivate the spleen and stomach, clear heat and detoxify, activate blood circulation and remove blood stasis, etc. Combined with data mining and analysis of clinical medication rules, it can more efficiently and scientifically start from the cause of the disease and precisely use medication to stop the disease process and reduce the pain for patients.

#### 3.1 Single-flavor drugs

Li [32] analyzed the medication pattern of gastric precancerous lesions in the past 10 years and concluded that deficiency tonics, heat-clearing drugs and blood-stasis activating drugs were commonly used, and were combined with qi-regulating drugs and dampness-diffusing drugs to add or subtract with evidence. Among them, the most frequently used single herbs were Bupleurum, Curcuma, Salvia, Atractylodes, and Semen/ Poria. Yang Tao [33] summarized the core drugs for the treatment of gastric cancer through data mining as Atractylodes macrocephala, Poria, Radix et Rhizoma Atractylodes, Radix et Rhizoma Polygoni, Radix et Rhizoma Glycyrrhizae, Coix Coix lacrymae, Chen Pi, Radix Astragali, Radix prunus ginseng, and Fried malt.

Summing up the clinical experience of doctors in treating gastric cancer, it is easy to find that the clinical treatment also focuses on nourishing the spleen and stomach and eliminating external evil. Prof. Qian Bo-wen took the general treatment principle of supporting the righteousness and promoting the flow of qi, and often used the drugs that benefit the qi and strengthen the spleen, such as Radix et Rhizoma Ginseng, Radix Astragali and Rhizoma Atractylodis Macrocephalae, together with the qi-activating drugs, such as Citrus Aurantium, Chen Pi and Citrus Aurantium [34]. Prof. Zhou Zhongying used anti-cancer and detoxification herbs such as Baihua snake tongue herb, vine pear root, cat's claw herb, and shidanwei as the treatment rule [35].

Through the study and collation of herbal medicines with anti-cancer effects on stomach, it was found that herbal medicines play important roles in reducing inflammatory response, repairing gastric mucosa, down-regulating gene expression, and inhibiting cell proliferation, respectively, as shown in Table 1, which briefly introduces the clinically used herbal medicines for clearing heat, tonifying deficiency, and activating blood circulation and resolving blood stasis.

The herb is used to clear heat, detoxify the body, and promote dampness and lymphatic flow; the herb is also effective in removing blood stasis; and the herb is used to clear dampness and heat in the middle jiao. Modern pharmacological studies suggest that the anthraquinones, flavonoids, terpenoids and steroids in *C. alba* can effectively inhibit the expression of gastric cancer cells [36, 37] and have good antitumor effects. Tian Hua [38] showed that dandelion polysaccharide

significantly downregulated the expression of ph-ERK1/2 and COX-2, reduced inflammatory damage, and promoted the repair of damaged mucosa in rat modeling. Yun-Yun Tsai [39] found that extracts of *Semen nigra* could interfere with tumor cell proliferation and metastasis.

*Atractylodes macrocephala*, *Astragalus membranaceus*, and *Radix Codonopsis pilosulae* are all important tonic for deficiency and have a high clinical use rate. *Atractylodes*, glycosides, polysaccharides, and amino acids contained in *Atractylodes macrocephala* mainly act in the gastrointestinal system and have anti-tumor and gastric mucosa repair effects [40]. Flavonoids, polysaccharides, and saponins, which are the main components of *Astragalus*, have various effects such as improving immune function, enhancing body metabolism, and anti-tumor [41]. Zhou J [42] found that *Astragalus* polysaccharides could reduce gastric mucosal lesions and inhibit gastric cancer cell proliferation in rats by reducing the expression of EGFR, COX-2, etc. through experiments. The polysaccharides, alkaloids, flavonoids and acids [43] in *Radix et Rhizoma Ginseng* are known to regulate gastrointestinal function, protect gastric mucosa, improve immunity and anti-tumor [44-46].

In the Qing Dynasty, Ye Tianshi's "Clinical Guide to Medical Cases" said, "Long-term pain in the ligaments, the qi and blood are suffocated". The method of activating blood circulation and resolving blood stasis provides direction for the treatment of precancerous lesions in the stomach. Danshen, safflower, Chuanxiong, Curcuma and Panax ginseng have the function of activating blood circulation and resolving blood stasis, breaking blood and stopping bleeding. Modern pharmacological studies have shown that Panax ginseng can improve gastric juice secretion, increase gastric mucosal blood flow, reduce the expression of proto-oncogene C-myc, and enhance the expression of oncogene P16 in rats [47]. Both dihydrotanshinone I and tanshinone IIA in *Salvia miltiorrhiza* have antitumor activity [48]. Wang Zhonghui [49] found that curcuminol inhibited tumor cell proliferation, promoted apoptosis, and blocked tumorigenesis development by regulating Bcl-2 protein and ERK/NF-KB signaling pathway. Cui Haoran [50] found through experiments that chuanxiongzin could also inhibit the activation of the corresponding pathways, causing apoptosis and autophagy in gastric cancer SGC-7901 cells and inhibiting their proliferation.

### 3.2 Chinese medicine compound prescriptions

Compound formulas include sutra formulas and modern medical practitioners' own formulas, and there are relatively more studies on compound formulas, and the monarchs of herbal formulas contain great wisdom, which is being gradually confirmed through modern pharmacology, as shown in Table 2. Liu Jiacheng [51] found that hemihsia diarrhea heart soup can affect changes in the microenvironment of gastric mucosal tissue and promote the expression of oncogenic molecules, thus affecting and blocking the development of GPLs. Dong [52] found that Shengyang Yigong Tang may interfere with the progression of GPLs by reducing the expression level of NF-KB and improving the state of gastric mucosa through a rat test. Zhu Jingru [53] found that Chai Shao Liu Jun Tang could improve atrophic gastric mucosal lesions, and the mechanism may be related to the inhibition of NF-KB/STAT1 abnormal activation and down-regulation of NF-KB, mRNA and STAT1 protein overexpression in gastric mucosal tissues. Zheng Xiaojia [54] added *Angelica paeoniae* powder significantly improved the atrophic state of gastric mucosa in CAG rats, down-regulated JAK2/STAT3 signaling pathway, and reduced inflammatory factor



production and apoptosis.

Self-prepared formulas which include Xinyu Gastric Granules [55] developed by Professor Jingri Xie can decrease serum gastrin levels and increase serum growth inhibitor levels, decrease serum ET-1 levels, inhibit HP and reverse the process of GPLs in patients with GPLs. Other therapies, such as anti-pigmentation granules [56], Yangzheng Dispersing Tang [57], Phlegm Dispersing Formula [58], and Spleen Strengthening and Stasis Dissolving Formula [59], have certain pharmacological basis and significant clinical efficacy.

### **3.3 Other therapies**

Acupuncture has good effect on improving the immunity and reducing inflammation. Chen Y [60] found that acupuncture of Foot San Li and Liang Men could improve the precancerous state of gastric mucosa in rats caused by MNNG and reduce the serum CE-A concentration. Foot San Li and Liang Men are widely used in gastric diseases and have the effect of improving immunity and nourishing positive energy [61]. Emotional therapy improves the patient's psychological state, gives positive psychological suggestion to relieve patient's anxiety and alleviates excessive concern about the condition, thus achieving a state of balance in the internal organs and smooth flow of qi and blood. Acupoint application therapy exerts its medicinal effect by stimulating local acupoints and absorbing external drugs, which has the effect of regulating the physiological functions of the internal organs and enhancing the immunity of the body. For example, the sites of Zhonggui and Tianshu are selected for external stimulation to relieve pain, subdue rebellion and stop vomiting, and the symptoms of precancerous lesions in the stomach of patients. "The ear is the gathering of the clan chakra", and acupoint stimulation through ear acupuncture point burying beans can achieve the effect of prevention and treatment of diseases.

## **4. Mechanism of TCM for GPLs**

Many studies have shown that TCM has the function of bi-directional and multi-targeted regulation of immune microenvironment of gastric cancer. In this paper, we discuss the possible mechanism of TCM in preventing and controlling gastric cancer by regulating tumor immune microenvironment from protecting gastric mucosa and delaying mucosal lesions, improving inflammatory microenvironment and inhibiting inflammatory cancer transformation, and inhibiting cancer cell proliferation and controlling cancer metastasis.

### **4.1 Protecting gastric mucosa and delaying mucosal lesions**

Gastric precancerous lesions are essentially the transformation of damage to the gastric mucosa, and inhibiting gastric mucosal lesions can prevent gastric carcinogenesis. Xu Tingting[62] found that Yi Qi and Spleen Formula could improve the atrophic state of gastric mucosa in CAG rats. Jiang Yan[63] found through their study that it could elevate the level of growth inhibitory hormone in gastric tissues of model rats, which could play a therapeutic role in GPLs. Bai Yuning [64] found that Jianshu Tongluo Detoxification Formula may regulate gastric mucosal epithelial cell apoptosis through NF-KB/COX-2 and NF-KB/Bcl-2 signaling pathways.

### **4.2 Control of inflammatory response and inhibition of inflammatory cancer transformation**

Wu Tingting[65] demonstrated through experiments that Yi Qi, Huayu and Detoxification Formula may control inflammatory response and inhibit cell proliferation by down-regulating factors such as IL-8 and IL-10. The downregulation of inflammatory factors such as IL-8 was more pronounced in patients in the Baicalin Tang combined with western medicine treatment group compared to the western medicine control group alone [66]. Guo Min[67] found that strengthening the spleen and activating stasis could inhibit the inflammatory-cancer transformation signaling pathway, upregulate the expression of related oncogenes as well as downregulate the expression of related pro-oncogenes, and block the transformation of the disease. By improving the soil and regulating the immunosuppressive microenvironment composed of inflammatory factors, TCM allows the suppression of inflammatory-cancer transformation.

4.3 Inhibition of cancer cell proliferation and control of cancer metastasis

Yu Zhihong[68] confirmed that the formula of eliminating phlegm and dispersing nodules had a good tumor suppressing effect through mouse test, which could down-regulate serum IL-8 and TGF-β concentrations and inhibit gastric cancer cell metastasis. Liu Jindi[69] found that Yixin Gastric Granules could reduce the expression of corresponding genes, inhibit abnormal cell proliferation, and block or reverse the progression of GPLs. Hexia diarrhea heart soup can down-regulate the expression of EGFR in the gastric mucosa of gastric precancerous lesions in rats, and play a role in regulating the proliferation of precancerous cells [70].

5. Summary

Gastric cancer has a high incidence rate, which seriously affects the quality of daily life and psychological status and brings great pain to patients. With the help of Western medical treatment technology, clinical examination is improved. With the help of TCM evidence-based treatment features, clinical symptoms can be improved and pathological processes can be reversed. Further improve the basic research on the pathogenesis of gastric precancerous lesions with the aim of providing precise target treatment for gastric precancerous lesions. In this study, the mechanism of action and immunological mechanism of TCM single and compound targets on gastric precancerous lesions were compiled and analyzed, hoping to increase clinical trials and mechanism research on TCM, acupuncture and TCM characteristic treatment on this basis, and to better demonstrate the unique advantages of TCM in treating gastric precancerous lesions.

Table 1 Single herbs for GPLs and their points of action

| Category    | Herbs  | Ingredients                                 | Target                                 |
|-------------|--|---|--|
| Antipyretic | Andrograp paniculata                               | andrographolide                             | Caspase-3、Bax、Bcl-2                    |
|             | (Burm.F) Nees Radix Actinidiae                     | PolysaccharideFrom Radix Actinidiae Argutae | p38、caspase-9、TNF-α、Snail、NF-κB        |
|             | Argutae Taraxacum                                  | Polysaccharide from Taraxacum               | ph-ERK1/2、iNOS、COX-2                   |
|             | mongolicum Scutellariae                            | mongolicum polysaccharides                  | tumor suppressor genesP53              |
|             | Barbatae Herba Hedyotis diffusa Sophora flavescens | apigenin-7-O-β-D-glucuronide Matrine        | TP53、PTEN、PIK3CA、MLH1、KRAS miRNA-93-5p |
|             | Ait.   |   |  |



|  |  |  |  |
|--|--|--|--|
|  | Moutan Cortex                              | paeonol  | NF-κB signaling pathway, MMP-2, MMP-9  |
|  | Portulaca oleracea                         | polysaccharides from Portulaca oleracea brusatol                       | Protein SGC7901 tumor cell   |
|  | Brucea javanica(L.) Merr. Rhizoma smilacis | smilax glabra extract  | Nrf2/HO-1 signaling pathway SGC-7901、BGC823 tumor cell   |
| Anti-dampness medicine                     | glabrae Cortex Magnoliae                   | Honokiol, magnolol   | Cyclin-D1, Cyclin-E, CDK-2, Bcl-2  |
| Diuresis and Dampness Remedies             | Officinalis Coix lacryma-jobi              | coix seed oil, coixenolide   | PRMT5-PI3K/AKT signaling pathway   |
| Inner-warming                              | L.seeds Poria cocos                        | Poria polysaccharide; evodiamine                                       | MGC803 tumor cell  |
| Tonic for deficiency                       | Evodia Rutaecarpa                          | Ginsenoside  | RIP1/RIP3/MLKL signaling pathway   |
|  | Panax ginseng                              | Atractylodis Atractylenolide, Glycosides, polysaccharides, amino acids | relieve abnormal glycolysis, MAPK、miR-125b/STARD13/NEU1 and Notch1 Antineoplastic repair of gastric mucosa |
|  | Macrocephalae Rhizoma; Radix Astragali     | Asragaloside IV  | P53、P65、BEGF Protein factor  |
| Chinese medicine to regulate Qi            | Citri Reticulatae                          | Tangerine  | STAT3 signaling pathway  |
| Hemostatic drugs                           | Pericarpium Panax notoginseng              | Notoginsenoside  | P53 Protein, JNK/ERK signaling pathway   |
| Blood-stasis activators                    | Curcuma zedoaria, Salvia miltiorrhiza      | curcumin Tanshinone IIA  | Bcl-2、CDK-4  |
|  | Corydalis                                  | dihydromyricetin   | COX-2 Protein, NF-κB signaling pathway   |
|  | yanhusuo saffron                           | crocin   | ERK/VEGFA/VEGFR2 signaling pathway   |
|  | Rhizoma Curcumae                           | Beta-elemene   | miRNA-320, HIF-1α signaling pathway  |
|  | Chuanxiong                                 | Tetramethylpyrazine  | miRNA-1323 , EGFR-ERK/PKB signaling pathway  |
|  | Rhizoma Pinellia ternata                   | pinellia ternata extract   | SGC-7901 tumor cell  |
| Cough medicine to reduce phlegm and asthma | Jackintheulpit tuber                       | Arisaema alcohol extract, Arisaema water extract, curcumin             | SGC7901 tumor cell HIF-1α Protein、Bcl-2、CDK-4  |
| Toxicidal insecticide                      | Fructus cnidii                             | osthole  | CASP-3   |

Table 2 Compounded formulas for the treatment of GPLs and their rationale

| Formulas                           | Components   | Mechanism of action   |
|------------------------------------|--|---|
| Banxia Xiexin decoction            | Radix Panax notoginseng, Radix Scutellariae, Radix Scutellariae, Radix Ginger, Radix Glycyrrhiza Uralensis, Radix Ginseng, Radix Dates | inhibit the expression of STAT3 pathway, Promote the expression of tumor suppressor genes |
| modified Chaishao LiuJun decoction | Radix Codonopsis Pilosulae, Atractylodes Macrocephala, Poria, Glycyrrhiza Glabra, Pericarpium Citri Reticulatae, Radix Bupleurum       | enhance Syk, downregulate survivin and mutant p53 expression                              |

|                            |   |   |
|----------------------------|---|---|
|                            | Chinense, Radix Paeoniae Alba, Radix Salviae Miltiorrhizae, Rhizoma Curcumae, Dandelion, Radix et Rhizoma Alba, Radix et Rhizoma Hallucis Radix Ginseng, Poria cocos, Rhizoma Atractylodis Macrocephalae, and Radix Glycyrrhizae  | improve the acidic microenvironment of the gastric mucosa by downregulating the expression of lactate related proteins and to cause lactic acid outflow       |
| Sijunzi decoction.         |   |   |
| Xiangshaliujunzi decotion  | Mu Xiang, Sand, Semen, Pericarpium Citri Reticulatae Ginseng, Atractylodes Macrocephala, Poria, Licorice  | inhibit the expression of p53   |
| Zuojin pill                | Huang Lian, Wu Zhuyu  | inhibit the expression of TGF- $\beta$ 1, PI3K, and their downstream signals p-Akt, p-mTOR, and P70S6K, promoting the expression of PTEN, LC3-II and Beclin-1 |
| Wangshi Lianpo decoction   | Made of Hou Pao, Chuan Lian, Acorus calamus, made of Semen, black bean curd, jiao gardenia, reed  | downregulating the expression of IL-6 and NF- $\kappa$ B  |
| Huangqi Jianzhong tang     | root Astragalus, cinnamon stick, white peony, ginger, jujube, caramelized   | upregulation of the expression levels of IFN- $\gamma$ , IL-10, and IL-17   |
| Huangqin decotion          | sugar Scutellaria baicalensis, Paeonia lactiflora, Glycyrrhiza glabra,  | downregulating the expression of IL-8   |
| ShengyangYiwei Decotion    | Jujube Astragalus, Radix Codonopsis, Rhizoma Atractylodis Macrocephalae, Poria, Licorice, Pericarpium Citri Reticulatae, Radix Bupleurum, Radix Bupleurum, Rhizoma Dulcis, Rhizoma Zeleniae, Rhizoma Huanglian Astragalus, Radix Codonopsis, Poria, Atractylodes, Salvia, Dendrobium, Angelica, Paeonia, Rhizoma Ligusticum Chuanxiong, Rhizoma Trigonella, Curcuma | Regulation of the expression of miR-26a and miR-32, downregulating the expression of NF-KB  |
| Xinwei particles           | longa, Semen Armeniaca Radix Codonopsis pilosulae, Radix lily of the valley, Ocimum sanctum, Citrus aurantium bark, Radix Salviae Miltiorrhiza, Curcuma   | downregulate the expression level of $\beta$ -catenin   |
| Xiaopi particles           | longa, Dandelion, Rhizoma alba Astragalus membranaceus, Semen   | reducing the methylation level of p16CpG island and subsequently upregulating its protein expression level  |
| Yangzhengsanjie decotion   | Nelumbinis, Fructus Foetida, Curcuma longa, Tenaxanthus, Cyperus rotundus, Hawthorn Semen, tiannanxing, zhebei, raw   | inhibit the expression of miRNA-7, promote the apoptosis of cells   |
| Huatansanjie decotion      | oyster, whole scorpion, dilong, shougong, squid bone, roasted licorice, wood butterfly, phoenix   | inhibit the growth of MKN45, affect cell proliferation  |
| Jianpi Huayu Jiedu formula | coat, hedgehog skin Radix Codonopsis Pilosulae, Radix Paeoniae Alba, Radix Angelicae  | downregulate $\beta$ -catenin protein accumulation by inhibiting the Wnt/ $\beta$ -catenin/GSK3 $\beta$ signaling pathway                                     |

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